(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number
WO 2004/007704 A3

(51) International Patent Classification[7]: C12N 9/02

(21) International Application Number:
PCT/EP2003/007744

(22) International Filing Date: 16 July 2003 (16.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
102 32 151.5 16 July 2002 (16.07.2002) DE

(71) Applicant *(for all designated States except US)*: **MAX DELBRÜCK CENTRUM FÜ MOLEKULARE MEDIZIN (MDC) BERLIN-BUCH** [DE/DE]; Robert-Rössle-Strasse 10, 13125 Berlin (DE).

(71) Applicant and
(72) Inventor *(for US only)*: **BADER, Michael** [DE/DE]; Strasse 45, Nr. 35, 13125 Berlin (DE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **WALTHER, Diego** [DE/DE]; Florapromenade 28, 13187 Berlin (DE).

(74) Agents: **KRAUSS, Jan, B.** et al.; Boehmert & Boehmert, Meinekestrasse 26, 10719 Berlin (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

(88) Date of publication of the international search report:
8 April 2004

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 2004/007704 A3

(54) Title: NEURONALLY EXPRESSED TRYPTOPHANE HYDROXYLASE AND ITS USE

(57) Abstract: The present invention relates to novel, specifically neuronal expressed proteins with tryptophane hydroxylase activity, nucleic acid sequences, recombinant nucleic acid molecules containing these nucleic acid sequences or vectors containing these nucleic acid sequences or the recombinant nucleic acid molecules encoding for a neuronal tryptophane hydroxylase. The invention also relates to transgenic organisms containing these nucleic acid sequences, the recombinant nucleic acid molecules or the above cited vectors. The invention moreover refers to mono- or polyclonal antibodies directed against the isolated proteins. Furthermore, the invention relates to the use of these nucleic acid sequences and proteins for diagnosis, predisposition, therapy and monitoring of neuronal diseases. Possible fields of application among others are medicine and the pharmaceutical industry.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07744

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N9/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/17891 A (MAX DELBRUECK CENTRUM ;BADER MICHAEL (DE); WALTHER DIEGO (DE)) 7 March 2002 (2002-03-07) the whole document | 1,2, 4-18, 20-28 |
| X | CHUNG Y I ET AL: "Immunochemical characterization of brain and pineal tryptophan hydroxylase" JOURNAL OF KOREAN MEDICAL SCIENCE, vol. 16, no. 4, August 2001 (2001-08), pages 489-497, XP009019879 ISSN: 1011-8934 abstract | 8,9 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 October 2003 | 13.01.04 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Sommer, B |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07744

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WALTHER D J ET AL: "Synthesis of serotonin by a second tryptophan hydroxylase isoform." SCIENCE (WASHINGTON D C), vol. 299, no. 5603, 3 January 2003 (2003-01-03), page 76, XP002259156 ISSN: 0036-8075 (ISSN print) the whole document | 1-18, 20-28 |
| P,X | WO 02/097039 A (LEXICON GENETICS INC) 5 December 2002 (2002-12-05) the whole document, in particular SEQ ID Nos. 1 and 2 | 1-18, 20-28 |
| A | CASH C D: "Why tryptophan hydroxylase is difficult to purify: A reactive oxygen-derived species-mediated phenomenon that may be implicated in human pathology" GENERAL PHARMACOLOGY, vol. 30, no. 4, April 1998 (1998-04), pages 569-574, XP002259157 ISSN: 0306-3623 abstract; page 569, right-hand column, second paragraph - page 570, left-hand column, second paragraph; | 1-18, 20-28 |
| T | WALTHER D J ET AL: "A unique central tryptophan hydroxylase isoform" BIOCHEMICAL PHARMACOLOGY, vol. 66, no. 9, 1 November 2003 (2003-11-01), pages 1673-1680, XP002259158 the whole document | 1-18, 20-28 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07744.

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-17, 23, 24 and 28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 10-15, 18
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see PCT/ISA/210 annex

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

---

Continuation of Box I.2

Claims Nos.: 10-15, 18

Present claims 10-15 and 18 relate to a compound defined by reference to a desirable characteristic or property, namely a to a snTPH polypeptide.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has only been carried out for those parts of the claims which appear to be clear, supported and disclosed, i.e. the terms "snTPH polypeptide" or "snTPH", respectively, have been interpreted as "a polypeptide according to claim 2". Furthermore, claim 14 has been interpreted for the purpose of an incomplete search as a method for the treatment of neuronal diseases characterised in that the serotonin production is decreased by ribozymes, antisense oligonucleotides or antisense RNA expression directed against a polypeptide according to claim 2.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-12, 15-18 and 20-28 (completely); 13 and 14 (partially)

an isolated nucleic acid sequence which encodes for a polypeptide with neuronal tryptophan hydroxylase activity as well as subject-matter related thereto;

1.1. claims: 1-12, 15-18 and 20-28 (completely); 13 and 14 (partially)

a nucleic acid sequence with SEQ ID No. 1, which encodes for a polypeptide according to SEQ ID NO. 2 as well as subject-matter related thereto;

1.2. claims: 1-12, 15-18 and 20-28 (completely); 13 and 14 (partially)

a nucleic acid sequence with SEQ ID No. 3, which encodes for a polypeptide according to SEQ ID NO. 4 as well as subject-matter related thereto;

1.3. claims: 1-12, 15-18 and 20-28 (completely); 13 and 14 (partially)

a nucleic acid sequence with SEQ ID No. 5, which encodes for a polypeptide according to SEQ ID NO. 6 as well as subject-matter related thereto;

---

2. claim: 13 (partially)

a method for the treatment of neuronal diseases characterised in that the serotonin production is increased by the addition of the precursor substance 5-hydroxy-tryptophan;

---

3. claim: 13 (partially)

a method for the treatment of neuronal diseases characterised in that the serotonin production is increased by the addition of substituted analogues of 5-hydroxy-tryptophan;

---

4. claim: 14 (partially)

a method for the treatment of neuronal diseases characterised in that the serotonin production is decreased by ribozymes;

---

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. claim: 14 (partially)

a method for the treatment of neuronal diseases characterised in that the serotonin production is decreased by antisense-oligonucleotides;

---

6. claim: 14 (partially)

a method for the treatment of neuronal diseases characterised in that the serotonin production is decreased by antisense RNA expression;

---

7. claim: 14 (partially)

a method for the treatment of neuronal diseases characterised in that the serotonin production is decreased by means of specific TPH-inhibitors like p-chlorophenylalanine or p-ethinylphenylalanine;

---

8. claim: 19 (completely)

a method of diagnosing a neuronal disease, characterised in that a specific inhibition of the peripheral serotonin biosynthesis is accomplished, followed by subsequently detecting the metabolite concentrations stemming from the CNS and by determining the severity of the disease via a comparative graph;

---

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/07744

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 0217891 A | 07-03-2002 | DE 10043124 A1 | 14-03-2002 |
| | | WO 0217891 A2 | 07-03-2002 |
| | | EP 1317265 A2 | 11-06-2003 |
| WO 02097039 A | 05-12-2002 | WO 02097039 A2 | 05-12-2002 |
| | | US 2002192694 A1 | 19-12-2002 |